REMARKS/ARGUMENTS

Amended claims 44 and 55 correspond to subject-matter of the original claims and subject-matter disclosed in the application as filed, see in particular page 14, lines 1-10. No new matter has been added to the claims.

Reconsideration and withdrawal of the rejections is rquestd. Should the above amendment not place this case in condition for allowance, an interview is requested.

Davies discloses an inhalation device that uses a medicament pack that comprises two sheets peelably secured to one another (paragraph [0004], [0041]). These two sheets define a plurality of medicament containers spaced along the length of the sheets (paragraph [0005]). These containers, typically 60 or 100 per pack, are formed recesses in a roll of the flexible, elongated strip/sheet, denoted base sheet (paragraph [0049]). The recesses are filled with powder and sealed with a common peel-off tape, denoted lid sheet (paragraph [0049]). In connection with inhalation, the two sheets are peeled apart a sufficient portion to expose the contents of a dose pocket, which is being brought into alignment with a slot that is in connection with a nozzle (paragraph [0050]).

The medicament pack described in Davies is **not** adapted for the special requirements noted in the pending claims in terms of a dry, moisture-tight, barrier seal for preventing ingress of moisture and thereby disruption of the fine particle fraction of the powder dose in the package.

In order for the medicament pack of Davies to be useful in an inhalation device, the seal between the two sheets must of course constitute the weakest part of the medicament pack in terms of physical strength. Thus, in order to be able to peel off the lid sheet from the base sheet before an inhalation action is performed by a user, the seal between the two sheets must

be broken relatively easily. Thus, a peelable blister design has several inherent weaknesses from a moisture protection point of view.

Firstly, the sealing area (land area) surrounding the blister cannot be made wide enough to prevent moisture from migrating through the inside plastic layers of the base foil and lid foil seal respectively, because it must be possible to separate the foils by peeling using moderate force. The foils must not break during peeling, which means that the base and lid foils must have tensile strength implicating a thicker plastic layer than desirable from a water vapor migration point of view (as the migration rate is directly proportional to plastic layer thickness).

Secondly, a peel-off design of a blister limits the choices of base and lid foils. If the base foil is made too stiff, it will cause problems in handling of the blister in the inhaler before and after the dose has been delivered. Further, if the sealing of the lid foil to the base foil is made too strong, the base foil will be deformed by the peeling force and may break as may the lid foil.

Thirdly, a peel-off seal is inherently weaker from a moisture penetration point of view as compared to a moisture-tight seal foil fixed to a dry, moisture-tight container to form a dry-moisture-tight, barrier seal (see for example, Borgström et al. "An In Vivo and In Vitro Compariosn of Two Powder Inhalers following Storage at Hot/Humid Conditions" *Journal of Aerosol Medicine*, **18**:309, 2005). The relatively thick PVC laminate layer required for providing the necessary physical strength of the peelable blister provides a route of water vapor migration into the dose contained therein. The rate of this water vapor migration is directly proportional to the PVC thickness. As the medical product of the present invention is not designed for any peelable opening solution, a much thinner PVC film, such as 15 μm, can be employed as moisture-tightness requirements, and not mechanical strength requirements, are a primary objective of the present invention. Thus, this means that usage of, for example,

a 15 μm PVC film as compared to the 100 μm PVC laminate of Davies would reduce the water migration six-fold. However, for mechanical and constructional point of view Davies is limited with usage of thick PVC laminates.

In addition, a hermetical seal does not necessarily have to be a moisture-tight seal. For example, the coefficient of permeation of water is about 50 000 times higher than the corresponding coefficient of permeation of air for PVC (the material employed by Davies) (see "Influence of packaging material to tightness packing material for pharmaceutical application" by Dr. Pasbrig, Erwin, August 13, 2006, ALCAN). Thus, even though Davies discusses forming a hermetical (defined as "airtight" by Merrian-Webster's Collegiate® Dictionary) seal, the seal and blister of Davies does **not** constitute a dry, moisture-tight, barrier seal as defined by the present invention and the amended claims for the reasons given in the foregoing and presented further below.

In a further aspect the method of filling the pockets is to pour powder onto the base tape and to use a doctor blade to remove surplus powder such that all pockets are completely filled before the lid sheet is applied. However, it is practically *impossible* to guarantee that no powder particles are left on the sealing surfaces of the base tape, which results in deficient seals from a moisture penetration point of view when the lid sheet is applied and heat-sealed.

The pockets are quite small in size (approximately half-cylindrical shape 6×3×1.5 mm = 16 mm^3) and it is impossible to reliably leak test every pocket in the tape or the whole tape, before releasing the tape pack to users. Further, since the medicament pack preferably comprises a multitude of pockets, the risk of releasing packs having defect pockets increases rapidly with increasing numbers of pockets. Thus, the peel-off type of medicament pack that is taught by Davies is suitable for multi-dose inhalers, where more than a few doses of medicaments impervious to moisture are included in the pack.

Thus, during in-use, significant amounts of moisture will leak through the foil into the blisters and to interact with the powder therein. This is often not a major problem for moisture-insensitive medicaments, but for tiotropium even *minute* amounts of moisture will dramatically affect the fine particle fraction of the powder dose. This in turn implies that the delivered fine particle dose will vary depending on the ambient conditions in which the medicament pack is stored and an exact, correct dosage will not be deliverable at each time of administration. As the skilled person understands, this is totally unacceptable from medical security and treatment point of views.

In addition, once the user has opened a secondary package (as marketed in the U.S.) containing an inhaler device pre-loaded with a medicament pack comprising a plurality of doses (see claim 14) according to Davies, moisture can migrate into all the powder doses in the pack and negatively affect the powder doses therein. As the skilled person is well aware of, it is today very hard to have a moisture-free internal environment in an inhalation device, including the inhalation device disclosed by Davies.

It is evident from the description of Davies that the medicament pack and inhalation device disclosed therein are not applicable for the moisture-sensitive tiotropium medicament. Furthermore, Davies is totally silent regarding the problems of moisture protection. Clearly, Davies is not aware of the extreme sensitivity of tiotropium to moisture, or he would not suggest to make a medicament pack of a multitude of tiotropium doses contained in receptacles sealed by a common, long strip of peel-off tape, i.e. the same construction as used for moisture-insensitive medicaments, such as fluticasone and budesonide.

The peelable container disclosed by Davies is actually present on the market today under the trade name Seretide DISKUS™ for the medicament combination of salmeterol and fluticasone propionate. Several investigations have been performed on this peelable container and its moisture-tightness. These investigations have concluded that the container has major

moisture problems and it is not tight enough to prevent ingress of moisture and thereby cannot preserve the FPD through the in-use time and shelf life of the DISKUS™ product. In clear contrast, the FPD has decreased with 68 % only after 1 month's storage at 40 °C/75 % Rh and with 78 % after 3 months in 25 °C/60 % Rh (see for example, Borgström et al. "An In Vivo and In Vitro Compariosn of Two Powder Inhalers following Storage at Hot/Humid Conditions" *Journal of Aerosol Medicine*, **18**:304-310, 2005).

In the U.S. these moisture problems have been regarded so severe that the DISKUS™ product has to be enclosed in a secondary outer protective pouch. The inhaler and peelable strip within this couch is sold as ADVAIR™ in the U.S.

The DISKUS™ product has also been marred by low FPD, in the order of merely 10 % in several different experiments (Borgström et al, "Idealhalers or realhalers? A comparison of Diskus and Turbohaler", *International Journal of Clinical Practice*, **59**:1488-1495, 2005). The moisture problems of the peelable container solution in the DISKUS™ product can be one of the causes behind such a low achievable FPD.

The powder medicaments used in these investigations and found in the DISKUS™ product (salmeterol and fluticasone propionate) are far less moisture-sensitive as compared to tiotropium. This means that these problems identified in the peelable container solution by Davies will be even more severe if a moisture-sensitive medicament as tiotropium is used.

In summary, the blister taught by Davies does not fulfill the features of the amended claims since the blister does not constitute a dry, moisture-tight, barrier seal and the blister does not prevent ingress of moisture into the powder dose.

Furthermore, the blister of Davies is not designed for enabling gradual aerosolization of the powder dose during a prolonged delivery. The blister has elongate pockets (paragraph [0042]) that are transversely arranged with regard to the lengths of the strip. This means that a pocket is opened sideways as the lid sheet is peeled off to provide access to the dose. All of

the powder in the dose is thereby exposed instantly to the ambient air. In addition, all the dose will simultaneously be exposed to an inhalation air stream (paragraph [0053] and Figs. 4a, 4b and 11]. The blister of Davies is therefore not designed to enable a gradual aerosolization of the dose during dose delivery.

In clear contrast, the medical product of the invention can be opened by piercing or cutting through the container or the container seal using a sharp tool inside the inhaler, and not peeling the sealing foil off the container. The present invention makes a gradual aerosolization possible by opening the container in a longitudinal fashion, thereby making the inhalation air stream access the dose powder gradually.

According to the reasoning presented above, Davies does not teach any medical product as defined by the amended claims.

Goede teaches a pharmaceutical powder cartridge holding a large number of powder doses in an inner storage space (paragraphs [0001], [0025], [0032], [0034], [0036], [0058]). The cartridge also includes an integrated metering device consisting of a slide channel, in which a metering slide can be moved from a filling position and an emptying position (paragraphs [0001], [0025], [0032], [0034], [0036], [0060], [0066]). At the filling position, a metering cavity of the metering slide is aligned with an outlet of the storage space to enable medical powder to fall from the storage place into the cavity (paragraph [0067]). The metering slide is then moved to position the cavity over an emptying opening to allow the metered powder to fall from the cavity through the opening into a powder channel of an inhaler (paragraph [0068]).

Goede identifies the moisture problem with the prior-art multi-dose cartridges and dry powder inhalers. In order to try to combat this moisture penetrating problem Goede firstly equips the cartridge with a dedicated internal metering device. This means that the powder storage and dose metering will take place within the cartridge unit. In addition, the movable

metering slide is equipped in a first end with an elastic seal for sealing off the slide channel from the environment when the slide is in the filling position (paragraphs [0025], [0027], [0029], [0034], [0060]).

Goede specifies that due to this cartridge design, the cartridge can be used in connection with moisture-sensitive pharmaceuticals, including tiotropium bromide (paragraphs [0045], [0046], [0049]).

Goede does not disclose a medical product having a moisture-tight seal foil fixed to a moisture-tight container to form a dry, moisture-tight, barrier seal. In clear contrast, the cartridge disclosed by Goede is actually incompatible with any usage of sealing foil due to the internal multi-dose storage space and the movable metering slide. In such a case, the metering cavity of the metering slide must be sealed with a sealing foil within the cartridge body and then shortly thereafter opened once more at dose delivery. This is not only technically infeasible but would then result in enclosing moisture present inside the cartridge body in the metering cavity, where it can negatively affect the sensitive pharmaceutical. This should be compared to the present invention, in which the medical product can be produced at controlled low humidity conditions. In fact, Goede admits that the disclosed cartridge does not totally seal off moisture and acknowledges that moisture will penetrate into the cartridge (paragraphs [0038], [0072]).

A skilled person will realize (as Goede has done, see paragraphs [0038] and [0072]) that moist air will unavoidably come in contact with the powder every time the empty metering cavity is to be filled with powder, since the air in the metering cavity is replaced by powder. The air and moisture contained in the air cannot go anywhere else but into the reservoir. If this was not the case then a low pressure will be created, which in the end will stop further filling operations, according to the teachings of Goede.

After delivery of the first dose of pharmaceutical in humid conditions, the air trapped inside the Goede cartridge is of course humid. The humid air will enter the storage space at least when a previously presented dose is measured and negatively affect the bulk of powder in the storage space, and humid air will also quickly affect a measured dose during transport to a location inside the cartridge from where the pharmaceutical dose will be aerosolized at some point in time thereafter.

In order to combat these problems, Goede suggests employing a desiccant inside the cartridge (paragraphs [0038], [0039], [0072]). Even if a desiccant is provided additionally to the elastic seal, any amount of moist air going past the elastic seal (as moist air will), at least when the metering slide is in the emptying position, the moisture will be adsorbed or absorbed by the desiccant, Goede hopes, but also by the pharmaceutical itself.

Thus, in summary, the cartridge of Goede does not contain any moisture-tight seal foil fixed to any moisture-tight container. The cartridge does not constitute a dry, moisture-tight, barrier seal. The invention as defined by the amended claims is therefore not unpatentable over Goede.

Zierenberg discloses an inhalation kit comprising inhalable powder of tiotropium. The active tiotropium substance, preferably in an amount of 0.001 to 5 %, is provided in admixture with a physiologically acceptable excipient (page 2, lines 17-19). Zierenberg discusses a micronized, inhalable powder of crystalline tiotropium bromide monohydrate in admixture with the excipient.

Zierenberg actually suggests filling the tiotropium powder into gelatin capsules, which constitute the medicament pack and are inserted into an inhalation device (page 5, lines 16-19). These described gelatine capsules are marred by the same moisture problems as the SPIRIVA® capsules tested in the present application. The reason for this is that gelatin *inherently* will contain a significant amount of water even after extensive drying.

Furthermore, drying makes the gelatin brittle, such that if dried too much, the capsule cannot be safely handled and opened by the inhaler without a substantial risk of breaking the capsule when the dose is about to be delivered to an inhaling user. Thus, a gelatin capsule used as powder container will contain at least about 10 % water by weight during the dose forming procedure. However, even if the capsule is exposed to an extensive drying operation, some water will still, due to the properties of gelatin, be enclosed in the gelatin matrix. This contained water will then leak into the capsule interior and negative affect the sensitive powder therein. Therefore, any form of gelatin capsule will be totally unsuitable for the extremely moisture-sensitive tiotropium medicament.

Zierenberg does not disclose a medical product comprising a moisture-tight seal foil that together with the container forms the dry, moisture-tight barrier seal of the medical product. In addition, due to the high moisture content enclosed in the gelatin capsule, this embodiment of Zierenberg does not disclose a medical product having a dry, moisture-tight barrier seal that prevents ingress of moisture into the dose or include a dry, moisture-tight container. On the contrary, the capsule (container) will indeed release moisture into the powder dose. As a consequence, this capsule embodiment cannot preserve the FPD during the in-use time and the self life of the medical product.

Zierenberg also mentions usage of multi-dose inhaler having a storage chamber containing multiple doses of the inhalable powder (page 7, line 25 – page 8, line 4). Such a solution is not compatible with moisture-sensitive powders since moisture present in the inhaler and/or leaking into the inhaler will interact with the powder, destroying the fine particle fraction of the powder. This inherent problem of multi-dose inhalers is well-known in the art as for example discussed by Keller et al. in US 2004/0202616 A1, shown by Maggi et al. in "Influence of the moisture on the performance of a Previously Presented dry powder inhaler", *International Journal of Pharmaceutics*, 177:83-91, 1999 and identified by Goede

in the foregoing. Therefore, such multi-dose inhaler solutions are not compatible with moisture-sensitive medicaments such as tiotropium.

Zierenberg does not disclose a medical product comprising a moisture-tight seal foil fixed to a container for forming the dry, moisture-tight barrier seal of the medical product. In addition, the multi-dose inhaler solution will not constitute a dry, moisture-tight barrier seal that prevents ingress of moisture into the dose. The reason for this is that moisture will penetrate into the multi-dose container through small openings between the inhaler parts. Keller discusses this problem by stating that powder mixtures that are sensitive to moisture in the surrounding air (such as tiotropium) are limitedly suitable for use in a multi-dose dry powder inhaler which contains a powder reservoir, since this is not a tight pack in the sense of a sealing-off of water vapor (paragraph [0016] of Keller). Zierenberg also mentions usage of a peelable sheet solution (page 9, line 35 – page 10, line 10). This solution is similar to what is disclosed by Davies described in the foregoing. As a consequence, the discussion of Davies applies mutatis mutandis to this embodiment of Zierenberg.

Zierenberg does not even mention moisture and its effect on a dose of tiotropium. In addition, there is no discussion of the implications of using dose containers having poor resistance to ambient moisture, or indeed, dose containers made of materials, which contain substantial amounts of free water that may be released inside the container under storage and when in use.

The Examiner has also cited a combination of Davies and Zierenberg against dependent claims of the invention. Such a combination would at most lead to usage of the powder composition suggested by Zierenberg, active tiotropium substance in admixture with a physiologically acceptable excipient, provided in the blister of Davies. However, as the blister of Davies does not disclose the medical product of the amended claims for the reasons

given above, such a combination of the two documents would not result in any medical product anticipating the present invention.

Keller discloses a dry powder formulation having improved moisture resistance and thereby being useful in a multi-dose dry powder inhaler (DPI) (paragraphs [0001], [0017], [0040]). The dry powder formulation consists of i) a pharmaceutically ineffective carrier of non-inhalable particle size, ii) a finely divided pharmaceutically active compound of inhalable particle size, and iii) magnesium stearate (paragraph [[0019], claims 22, 43, 44). Instead of employing a single pharmaceutically active compound, two or more such pharmaceutically active compounds can be used together with the carrier and magnesium stearate (paragraphs [0027], [0029], [0038], claim 58). Keller further lists several useful pharmaceutically active compounds, including beta-mimetics (such as formoterol fumarate, salbutamol sulfate, salmeterol xinafoate), anticholinergics (such as tiotropium bromide, ipratropium bromide, oxitropium bromide) and corticosteroids (such as fluticasone propionate, budesonide) (paragraphs [0027], [0029]).

The magnesium stearate adds several advantages to the powder formulation in terms of minimizing the influence of penetrating moisture on MMAD, FDP and FPF during storage and delivery, stabilizing the carrier material and the active compound (paragraphs [0017], [0018]). This increase in moisture resistance allows the formulation to be used in a multi-dose DPI, where otherwise penetrating moisture is a major problem (paragraphs [0007], [0016], [0040]).

Thus, Keller does not disclose or even suggest sealing the dose by a moisture-tight, seal foil to thereby prevent ingress of moisture. The solution presented by Keller is actually incompatible with using a seal foil for sealing the dose. In Keller's multi-dose DPI individual doses of a powder composition is metered from a bulk store insider the inhaler to a metering receptacle shortly before inhalation. Such a technical solution is not compatible with usage of

sealing foils (see discussion above in connection with Goede). In clear contrast, Keller adds the generated powder formulation to a bulk powder store of a multi-dose DPI, where ingress of moisture is a major problem (see paragraph [0016] in Keller).

The Examiner has cited a combination of Goede and Keller against the present invention. This combination would at most amount to employing the dry powder formulation proposed by Keller in the cartridge of Goede. However, as neither of the solutions presented in these documents are compatible with a medical product having a moisture-tight seal foil fixed to a dry, moisture-tight container a combination of the documents will not anticipate the present invention as defined by the amended claims.

As shown by the above analysis of the references, no reference alone or in combination with any other reference(s) renders the present claims unpatentable. There is no disclosure of the claimed subject matter, nor is the claimed subject matter rendered obvious. The rejections should be withdrawn.

Finally, the Examiner has made several provisional double patenting rejections. It is submitted that the claims in this case can be passed to Issue in order to first form a firm basis for comparison, after which actual double patenting rejections may be made in the co-pending applications if appropriate during prosecution.

Respectfully submitted,

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